Cancers -- Adenocarcinoma and Neuroendocrine: Screening High Risk Groups and New Neuroendocrine Tumor Guidelines

Robert C. Kurtz, MD, FACG
Gastroenterology/Nutrition Service
Memorial Sloan-Kettering Cancer Center
New York, NY

Pancreatic Ductal Adenocarcinoma (PDCA) is a Lethal Disease
Robert C. Kurtz, MD, FACG

PDCA
Incidence and Mortality

2013

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>22,740</td>
<td>22,480</td>
<td>45,220</td>
</tr>
<tr>
<td>Mortality</td>
<td>19,480</td>
<td>18,980</td>
<td>38,460</td>
</tr>
</tbody>
</table>

ACS, Facts & Figures, 2013

PDCA

Once symptoms develop, chance for cure is small.
The overwhelming majority of patients present with advanced stage disease.
**PDCA**

*All Stages Combined*

1-year survival rate = 19%

5-year survival rate = 4%


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**PDCA**

*Stage and Survival*

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable Disease</td>
<td>12 to 20 months</td>
</tr>
<tr>
<td>Locally Advanced Disease</td>
<td>6 to 10 months</td>
</tr>
<tr>
<td>Metastatic Disease</td>
<td>3 to 6 months</td>
</tr>
</tbody>
</table>

*AJCC Cancer Staging Handbook, 6th ed*
Resected PDCA
*MSKCC 1983-2005 (n=970)*

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA: T1, N0</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td>IB: T2, N0</td>
<td>168 (17.5)</td>
</tr>
<tr>
<td>IIA: T3, N0</td>
<td>190 (19)</td>
</tr>
<tr>
<td>IIB: Tany, N1</td>
<td>597 (62)</td>
</tr>
</tbody>
</table>

**Risk Factors for PDCA**

- Age
- Gender
- Race
- Diabetes Mellitus
- Occupation
- Family History
- Pancreatitis
- Cigarette Smoking
Cigarette Smoking is the Most Consistent Risk Factor for PDAC

Smokers have a 2- to 3-fold increase in pancreatic cancer
Smoking may be implicated in as many as 30% of pancreatic cancers
Promotion of pancreatic cancer in familial patients
Risk decreases when smoking ceases (49% within 2 years)


PDCA

Family History:
Relative risk about 1.5-2
Strongly increased risk in families with multiple cancers

Diabetes:
Long-standing increases risk
Relative risk 1.5-2.0
Newly-diagnosed diabetes can be a sign of PDCA

Chronic Pancreatitis:
A strong but uncommon risk factor
Risk may be increased 15-fold
PDCA can be Familial

A family history of pancreatic cancer is found in about 10% of patients with pancreatic cancer.


Familial PDCA
Associated Known Syndromes

Heritable Breast - Ovary Cancer (BRCA2)*
Hereditary Pancreatitis (PRSS1)
HNPCC/Lynch II (hMSH2 and hMLH1)
Peutz-Jeghers Syndrome (STK11/LKB1)
(FAMMM) Familial Atypical Multiple Mole Melanoma Syndrome: p16 (CDKNA2)
Cystic Fibrosis

*The most common associated genetic abnormality found in families with two or more affected relatives.
### PDCA Risk

<table>
<thead>
<tr>
<th>Individual</th>
<th>Risk</th>
<th>Age 50 years (%)</th>
<th>Age 70 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Fam Hx</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>BRCA2</td>
<td>3.5-10x</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>FAMMM p16</td>
<td>20-34x</td>
<td>1.6</td>
<td>16</td>
</tr>
<tr>
<td>Hereditary Pancreatitis</td>
<td>50-80x</td>
<td>2.5-4</td>
<td>24-40</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>72x</td>
<td>6.6</td>
<td>36</td>
</tr>
</tbody>
</table>

**Should We Screen High-Risk Groups for PDCA?**
Who Should We Screen for PDCA? Enriched Populations

- New onset of diabetes mellitus
- Idiopathic pancreatitis
- New diagnosis of chronic pancreatitis
- Clinical depression
- Cigarette smokers
- Family history of PDCA

Principles of Cancer Screening

<table>
<thead>
<tr>
<th>Screening Principle</th>
<th>Colorectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common condition</td>
<td>Yes</td>
</tr>
<tr>
<td>Recognizable latent or asymptomatic phase (precursor lesion)</td>
<td>Yes, Colon Polyp</td>
</tr>
<tr>
<td>Reliable, valid, reproducible test</td>
<td>Yes, Colonoscopy</td>
</tr>
<tr>
<td>Easy to perform</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitive and specific test</td>
<td>Known</td>
</tr>
<tr>
<td>Low cost</td>
<td>Relatively</td>
</tr>
<tr>
<td>Effective treatment</td>
<td>Yes</td>
</tr>
<tr>
<td>Agreed policy on who to screen</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Screening for PDCA and Its Precursor Lesions

Screening members of Familial Pancreatic Cancer (FPC) families is not routinely performed.

(In a prospective cohort study, 21 of 22 incident pancreatic cancers that developed in relatives of probands were metastatic at presentation.)


PDCA Precursor Lesions

Pancreatic Intraepithelial Neoplasia (PanIN)

Intraductal Papillary Mucinous Neoplasms (IPMN)
Mucinous Cystic Neoplasms
Progression Model - Pancreatic Duct Lesions

Oncogene
K-ras
Telomerase

Flat duct
Lesion
PanIn-1A

Papillary duct
lesion
PanIn-1B

Papillary duct
lesion + atypia
PanIn-2

Ca in situ
PanIn-3


Oncogene
K-ras
Telomerase

Flat duct
Lesion
PanIn-1A

Papillary duct
lesion
PanIn-1B

Papillary duct
lesion + atypia
PanIn-2

Ca in situ
PanIn-3


PDCA Timeline

Histologic Progression

Normal
Duct
Histology
PanIN-1
IPMN
mild
dysplasia
PanIN-2
IPMN
mod
dysplasia
PanIN-3/
PanCa
IPMN
severe
dysplasia

Genetic Progression

Screening Window
MSKCC
FPC Screening Program

Aim
To determine if screening unaffected at-risk relatives in familial pancreatic cancer families is feasible and can identify premalignant lesions or early stage pancreatic cancer.
Methods

Unaffected at-risk relatives of FPC families are offered screening with either MRCP or CT scan every one to two years.

Abnormalities found on cross-sectional imaging studies are reviewed by a multidisciplinary team, and, when indicated, are further evaluated by endoscopic ultrasonography (EUS).

Screening At-Risk FPC Relatives

- **255** Screening offered
  - 23 Ineligible
  - 28 Considering
  - 136 agree
  - 68 Refused
  - 23 Pending
  - 113 screened

Screening compliance = 59%
Screening for Pancreatic Cancer and Its Precursor Lesions

<table>
<thead>
<tr>
<th>Pt</th>
<th>1°/2°</th>
<th>Imaging</th>
<th>EUS</th>
<th>SurgPath</th>
</tr>
</thead>
<tbody>
<tr>
<td>67/F</td>
<td>1/1</td>
<td>IPMN</td>
<td>IPMN</td>
<td>IPMN</td>
</tr>
<tr>
<td>86/F</td>
<td>2/0</td>
<td>IPMN</td>
<td>IPMN</td>
<td>IPMN</td>
</tr>
<tr>
<td>58/F</td>
<td>2/0</td>
<td>AdenoCa</td>
<td>AdenoCa</td>
<td>AdenoCa (T3N0)</td>
</tr>
<tr>
<td>63/F</td>
<td>1/3</td>
<td>Islet Cell</td>
<td>-------</td>
<td>Islet Cell</td>
</tr>
<tr>
<td>52/F</td>
<td>2/0</td>
<td>9mm cyst</td>
<td>Likely Branch-duct IPMN</td>
<td>-------</td>
</tr>
<tr>
<td>54/F</td>
<td>1/1</td>
<td>Tubular cystic structure, dilated side branch</td>
<td>Likely IPMN</td>
<td>-------</td>
</tr>
<tr>
<td>46/F</td>
<td>1/1</td>
<td>0.5mm cystic tail lesion</td>
<td>MCM</td>
<td>PANIN-2, focal fibrosis, chronic inflammation</td>
</tr>
<tr>
<td>73/F</td>
<td>2/0</td>
<td>Multiple small cysts</td>
<td>Likely IPMN</td>
<td>-------</td>
</tr>
</tbody>
</table>

FPC Screening Studies

<table>
<thead>
<tr>
<th>Author/year/site</th>
<th>n</th>
<th>Methods</th>
<th>Yield</th>
<th>Pathology (surg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentnall/1999/UW (prospective cohort)</td>
<td>14</td>
<td>Hx, ERCP, EUS, tumor markers</td>
<td>7 pts had abnormalities; 50%</td>
<td>N=7; diffuse PanIN</td>
</tr>
<tr>
<td>Canto/2006/JHH (prospective cohort, controlled) (CAPS2)</td>
<td>78</td>
<td>CT+EUS FNA, ERCP</td>
<td>78% underwent FNA; 10%</td>
<td>N=8; 1 cancer, 2 islet cell, 1 SCA</td>
</tr>
<tr>
<td>Ludwig/2009/MSKCC (prospective cohort)</td>
<td>113</td>
<td>34=CT/MR+EUS 79=CT/MR alone</td>
<td>1 advanced ca; 7 neoplastic lesions (8.3%)</td>
<td>N=5; 1 cancer, 3 IPMN, 1 islet cell tumor</td>
</tr>
<tr>
<td>Poley/2009/Netherlands (prospective cohort)</td>
<td>44</td>
<td>EUS→CT/MRI</td>
<td>Cancer = 7% IPMN = 16%</td>
<td>Cancers had N1 disease</td>
</tr>
<tr>
<td>Langer/2009/Marburg (prospective cohort)</td>
<td>76</td>
<td>EUS + MRCP</td>
<td>7 had surgery 10%</td>
<td>2 PANIN 1 and 2 1 IPMN 3 Serous cysts</td>
</tr>
</tbody>
</table>

Conclusions

It is feasible to offer screening to at-risk FPC relatives.
Compliance with screening is 59%.
MRCP-based screening can detect pancreatic neoplasia in at-risk relatives at a rate of about 1 in 15 screened individuals.
IPMNs may represent common precursor lesions found in at-risk FPC relatives.
**FPC Screening Conclusions**

<table>
<thead>
<tr>
<th></th>
<th>Colon Cancer</th>
<th>PDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease prevalence</td>
<td>50 per 100k</td>
<td>10 per 100k</td>
</tr>
<tr>
<td>Recognizable pre-</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>symptomatic phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening improves</td>
<td>Yes</td>
<td>Not Shown</td>
</tr>
<tr>
<td>survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Availability</td>
<td>Wide Availability</td>
<td>Few Major Centers</td>
</tr>
<tr>
<td>Accepted screening test</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ease</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Cost</td>
<td>Reimbursed</td>
<td>Not Reimbursed</td>
</tr>
<tr>
<td>Yield</td>
<td>15-25%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Benefits&gt;Risks</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Non-surgical treatment for precursor lesions</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Changes in FPC Screening MSKCC**

As a result of these findings, we have recently altered our study eligibility requirements to include only those individuals who have multiple first-degree relatives with PDCA, and those with a both a family history of PDCA and a deleterious BRCA 1 or 2 mutation, or Lynch Syndrome.
Neuroendocrine Tumors (NETs)

**Foregut** = bronchus, thymus, esophagus, stomach, duodenum, upper jejunum, biliary tract, and pancreas (pNETs)

**Midgut** = lower jejunum, ileum, appendix, cecum, and proximal colon

**Hindgut** = distal colon and rectum

*Heterogeneous tumors in each category, but trends in regards to response to therapies are seen.*

The Incidence of NETs is Increasing


NET Primary Site

If primary location is in the pancreas -> **pNET** (formerly known as islet cell carcinoma)

If primary location is outside the pancreas (most commonly in aerodigestive tract) -> **carcinoid tumor**

*And...primary site matters when considering medical therapy*

Prognosis of pNet is Related to **Morphology and Grade**

### Histologic Classification of (pNETs)

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic Count</th>
<th>Ki-67 index (%)</th>
<th>Traditional Classification</th>
<th>ENETS, WHO Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td>Low (G1)</td>
<td>&lt; 2 per 10 HPF</td>
<td>≤ 2</td>
<td>Carcinoid, islet cell, pancreatic neuroendocrine tumor</td>
<td>Neuroendocrine tumor, grade 1</td>
</tr>
<tr>
<td></td>
<td>Intermediate (G2)</td>
<td>2-20 per 10 HPF</td>
<td>3-20</td>
<td>Carcinoid, atypical carcinoid, islet cell, pancreatic neuroendocrine tumor</td>
<td>Neuroendocrine tumor, grade 2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High (G3)</td>
<td>&gt; 20 per 10 HPF</td>
<td>&gt; 20</td>
<td>Small cell carcinoma, Large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, small cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neuroendocrine carcinoma, grade 3, large cell</td>
</tr>
</tbody>
</table>

ENETS, European Neuroendocrine Tumor Society; WHO, World Health Organization; HPF, high-power fields.

**POORLY DIFFERENTIATED NETS ARE MANAGED WITH PLATINUM-BASED THERAPY AND ARE CONSIDERED AGGRESSIVE**

Klimstra, et al. *Pancreas* 2010
Treating pNETs

Surgery

Nonsurgical Liver-Directed Therapy
• Embolization (± chemotherapy)

Medical Treatment
• Somatostatin analogues
• Alpha interferon therapy
• Cytotoxic chemotherapy
• Biologic targeted agents
• PRRT*

*Peptide Receptor Radionuclide Therapy – (still considered investigational)
Controlling pNET Hormone Related Symptoms

1. Treat the tumor
2. Supportive agents - syndrome dependent
   - Anti-diarrheal agents
   - Somatostatin analogs - dose? Escalate?
   - PPIs
   - Glucose control

Octreotide LAR Provides Effective Symptom Relief

Median Number of Stools / Day

Baseline: 4.3
Week 24: 2.5

42% Reduction in Diarrhea Frequency

Median Number of Flushings / Day

Baseline: 4.5
Week 24: 0.7

84% Reduction in Flushing Frequency

References:

Medical Treatment of pNETs
**mTOR* Inhibition in NET**

- Original hypotheses derived clinically - patients with inherited problems of mTOR inhibition (TSC1/2) went on to develop NETs.
- Whole genome sequencing pNET - 15% mutations identified along mTOR pathway.
- Everolimus (RAD001) was FDA approved for pNET in April 2011.
- Whole genome sequencing small bowel NETs also reveal mutations along mTOR pathway.

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**The NEW ENGLAND JOURNAL of MEDICINE**

**Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors**
Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

**Everolimus for Advanced Pancreatic Neuroendocrine Tumors**
**RADIANT-3**
Progression-Free Survival by Investigator Review

- **Kaplan-Meier median progression-free survival**
  - Everolimus: 11.0 months
  - Placebo: 4.6 months

  - HR (stratified unadjusted Cox model) = 0.35; 95% CI 0.27-0.45
  - \( P \) (one-sided log-rank test) < 0.0001

**Sunitinib Phase III Trial**
Progression-Free Survival and ORR

- **RECIST**
  - Sunitinib: CR/PR 9%, SD 63%, PD 14%
  - Placebo: CR/PR 0%, SD 60%, PD 27%

  - Progression-Free Survival: 11.5 months vs 5.5 months


**ORR, objective response rate; CR/PR, complete response/partial response; SD, stable disease; PD, progressive disease.**
Medical Treatment Outlook for Advanced pNETs in 2013

- **Functional**
  - Somatostatin Analog

- **Nonfunctional, Stable Disease, or Low Volume**
  - Expectant Management
  - Somatostatin Analog
  - Everolimus
  - Sunitinib
  - Chemotherapy*

- **Nonfunctional and Disease Growth with Symptoms or High Volume Disease**
  - Radiolabeled Somatostatin Analog Therapy

*Generally for high tumor burden

**Radiolabeled Somatostatin Analog Therapy**

Octreotide Radiotherapy - yttrium ($^{90}$Y), lutetium ($^{177}$Lu)

- $^{90}$Y-DOTA tyr3-octreotide ($^{90}$Y-edotretide, $^{90}$Y-DOTA-TOC)
  - 1109 patients disease progression within 12 months
  - 34% “morphologic response”
  - 15% biochemical response
  - 29% symptomatic response
  - Grade 3-4 toxicities: 12% hematologic; 9% fatal renal toxicity

- $^{177}$Lu-DOTA, Tyr3-octreotate
  - 500 patients – efficacy reports on 310
  - Tumor response 30%

Treating pNETs

Surgery

Nonsurgical Liver-Directed Therapy
• Embolization (± chemotherapy)

Medical Treatment
• Somatostatin analogues
• Alpha interferon therapy
• Cytotoxic chemotherapy
• Biologic targeted agents
• PRRT

Conclusions

Somatostatin analogs should be given to the patient with functional tumors (i.e., hormonal-related symptoms). Other supportive medications (i.e., anti-diarrheal agents should also be encouraged).

Somatostatin analogs also appear to have an antiproliferative effect in midgut carcinoid; whether to start in the asymptomatic patient without evidence of disease growth is controversial.

Sunitinib and everolimus are FDA-approved for pNETs. Both targeted agents improve PFS. They are not approved for extra-pancreatic (i.e., carcinoid) tumors.
Cytotoxic chemotherapies should be considered an option in pNET patients with progressive disease on octreotide therapy (carcinoid tumors have a much lower chance of responding).

Clinical trial enrollment and novel therapeutic strategies are critical for bettering our understanding of pNETs.

pNETs require a team approach.